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Duloxetine versus Routine Care in the Long-Term Management of Diabetic Peripheral Neuropathic Pain

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ABSTRACT

Introduction: **Duloxetine hydrochloride is a dual reuptake inhibitor of both serotonin and norepinephrine. In the present open-label study, the safety of duloxetine at a fixed-dose of 60 mg twice daily (BID) for up to 52 weeks was evaluated and compared to routine care in the therapy of patients diagnosed with diabetic peripheral neuropathic pain (DPNP).**

Methods: **Patients who completed a 13-week, double-blind, duloxetine and placebo acute therapy period were rerandomly assigned in a 2:1 ratio to therapy with duloxetine 60 mg BID ($N = 161$) or routine care ($N = 76$) for an additional 52 weeks. Routine care consisted primarily of gabapentin, amitriptyline, and venlafaxine. The study included male or female outpatients 18 years of age or older with a diagnosis of DPNP caused by type 1 or type 2 diabetes.**

Results: **A higher percentage of routine care-treated patients experienced 1 or more serious adverse events. No statistically significant therapy-group difference was observed in the overall incidence of treatment-emergent adverse events (TEAEs). The TEAEs reported by 10% or more of duloxetine 60 mg BID-treated patients were nausea, and by the routine care-treated patients were peripheral edema, pain in the extremity, somnolence, and dizziness. Duloxetine did not appear to adversely affect glycemic control, lipid profiles, nerve function, or the course of DPNP. There were no statistically significant therapy-group differences observed in the 36-item Short-Form Health Survey subscales or in the EuroQol 5-Dimension Questionnaire.**

Conclusions: **In this study, duloxetine was safe and well tolerated compared to routine care in the long-term management of patients with DPNP.**

INTRODUCTION

DIABETES MELLITUS is a common disease, affecting approximately 6.3% (18.2 million) of the population in the United States.[1] Approximately 30%–60% of patients with diabetes develop long-term complications of peripheral neuropathy, and up to 10%–20% of these patients experience pain.[2–4] This pain is often described as an "aching, burning, stabbing, or tingling" sensation[3] and is characterized by hyperalgesia, paresthesia, and allodynia.[5–7]

The neurotransmitters serotonin (5-HT) and norepinephrine (NE) have been implicated in the modulation of endogenous analgesic mechanisms via the descending inhibitory pain path-

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ways in the brain and spinal cord.[8,9] In pathologic pain states, these endogenous pain inhibitory mechanisms may be dysfunctional. This may contribute to the central sensitization and hyperexcitability of the spinal and supraspinal pain transmitting pathways that may manifest as persistent pain.[10]

Tricyclic antidepressants (TCAs) with reuptake inhibitory activity for both 5-HT and NE have been widely used in the management of DPNP.[11,12] Hypothetically, dual reuptake inhibitors unburdened by the undesirable pharmacologic effects of TCAs should be better tolerated and more effective in managing diabetic peripheral neuropathic pain (DPNP). This hypothesis is supported by the finding that amitriptyline (5-HT and NE reuptake inhibitor) is superior to desipramine (NE reuptake inhibitor), which is superior to fluvoxamine (5-HT reuptake inhibitor) in providing pain relief.[13] In a crossover study comparing 4-week treatment periods, venlafaxine and imipramine were found to be superior to placebo in relieving DPNP.[14] Other drugs reported to manage DPNP are "anticonvulsants,"[15,16] selective serotonin reuptake inhibitors,[17] controlled-release oxycodone,[18,19] and the synthetic cannabinoid CT-3.[20]

Duloxetine hydrochloride (Cymbalta®, Eli Lilly and Company, Indianapolis, IN) is a selective 5-HT and NE reuptake inhibitor that is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition.[21] Because central sensitization is believed to be involved in the development and maintenance of chronic neuropathic pain, including DPNP, patients with DPNP may benefit from duloxetine therapy. Duloxetine (40 to 120 mg daily) has been shown to be safe and effective in the treatment of major depression.[22–26] Duloxetine is the first Food and Drug Administration (FDA)-approved prescription drug for the management of DPNP. In a randomized, controlled, 12-week trial comparing duloxetine 60 mg once daily (QD) and duloxetine 60 mg twice daily (BID) or duloxetine 20 mg QD with placebo in 457 patients with DPNP and without depression, duloxetine was found to be effective and safe for DPNP management.[27] Based on this evidence, two more independent 12-week acute therapy studies were conducted, and these studies confirmed the safety and efficacy of duloxetine 60 mg QD and 60 mg BID in the management of patients with DPNP.[28,29] The study presented here was conducted in order to evaluate the safety, as well as the impact of therapy on patient-reported health outcomes with up to 65 weeks exposure with duloxetine 60 mg BID or routine care. It is a one-year extension of an acute study, the results of which were previously reported.[28]

Study objectives

The objectives of this study were to evaluate the safety of duloxetine 60 mg BID over a 52-week open-label extension period, to evaluate the safety of duloxetine 60 mg BID for up to 65-week exposure with regard to the progression of diabetic complications, and to assess the impact of treatment with duloxetine 60 mg BID and routine care on patient-reported health outcomes.

METHODS

Study design and treatments

This study was a 52-week, randomized, open-label, extension trial comparing duloxetine and routine care in patients with DPNP. This multicenter study included 26 principal investigators, and was conducted at 27 investigative sites in the United States and Puerto Rico. The acute therapy phase of this study was 12 weeks in duration, with an additional 1-week drug-tapering phase. The extension therapy phase was 52 weeks, making the total duration of the study 65 weeks. Only those patients who completed the acute period of the study, independent of treatment assignment, were allowed to continue into the extension phase of the study. Patients were rerandomized (2:1) to either duloxetine therapy or routine care. Patients rerandomized to the duloxetine therapy group began on 60 mg QD for 3 days and then received 60 mg BID until 1 week prior to week 52 of the extension phase of the study, at which time the patient was instructed to reduce the dose of duloxetine to 60 mg QD. Patients could reduce their dose of duloxetine to 60 mg QD if they could not tolerate a dose of 60 mg BID.

Duloxetine was provided as 30-mg capsules and patients were instructed to take 4 capsules orally each day. Patients were seen after 1 week (week 14) of treatment with either duloxetine or routine care. They were then seen again at weeks 17, 21, 25, 33, 41, 49, 57, and 65 of treatment. Compliance was defined as taking between 80% and 120% of the study medication prescribed for each interval.

The routine care group was treated with therapies that the investigator and the patient believed permitted the optimal benefit to the patient. The duloxetine-treated patients received most therapies, including nonmedicinal therapy offered to the routine care group, with the exception of antidepressants, anticonvulsants, and antipsychotics. During this period, patients in both treatment groups were permitted to supplement their analgesia with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or opioid analgesics.

The ethical review boards provided approval of the study protocol in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent after the study was explained and prior to the performance of any protocol procedures and administration of the study drug.

Entry criteria

As detailed in Raskin et al.,[29] patients were eligible for the study if they were 18 years or older, and presented with pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. The pain had to begin in the feet and with relatively symmetrical onset. The daily pain should have been present for at least 6 months; neuropathy was confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI).[30] Patients had to have a mean score of 4 or more when assessed by 24-hour average pain severity on an 11-point Likert scale, stable glycemic control, and a glycosylated hemoglobin (HbA_{1c}) of 12% or more. Some of the reasons for patient exclusion were serious or unstable illness, current ($\leq$1 year) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I diagnosis of major depressive disorder, historical exposure to drugs known to cause neuropathy, a positive urine drug screen for substances of abuse, or excluded medication.

Safety assessments

Safety of duloxetine over the 52-week open-label extension period was measured by discontinuation rates, treatment-emergent adverse events (TEAEs), laboratory assessments, including lipid profile and glycosylated hemoglobin (HbA_{1c}), weight, and electrocardiograms (ECGs). A TEAE was defined as an event that first occurred or worsened after random assignment. Vital signs including heart rate and blood pressure were recorded. A patient considered to have sustained elevation in blood pressure after randomization met the following criteria: sitting diastolic blood pressure 85 mm Hg or more and increase from baseline of 10 mm Hg for 3 consecutive visits, or sitting systolic blood pressure 130 mm Hg or more and increase from baseline of 10 mm Hg for 3 consecutive visits.

The safety of duloxetine for up to 65 weeks was also evaluated with regard to the progression of diabetic complications, as measured by the MNSI (neuropathy progression), electrophysiology assessments (measures included ulnar F-wave, ulnar distal sensory latency, peroneal F-wave, peroneal compound muscle action potential [CMAP]), microalbumin/creatinine ratio (nephropathy progression), and an ophthalmologic examination (measures for retinopathy progression included worsening of visual acuity, procedures required, reasons for photocoagulation, and reasons for vitrectomy). Changes from baseline to endpoint were assessed where baseline refers to values collected prior to the acute therapy phase, and endpoint refers to values collected at week 65 of treatment or at an early discontinuation visit between week 41 and week 65 of treatment.

All data were collected at week 65 of treatment or at an early discontinuation visit between weeks 14 and 65 of treatment. In addition, data on vital signs, adverse events, and concomitant medications were collected at each visit starting from week 14 until week 65 of treatment, ECG data were collected at weeks 14 and 49 of treatment, and samples for HbA_{1c} and clinical chemistry profiles were collected at week 49 of treatment.

Health outcome measures

The impact of therapy with duloxetine 60 mg BID and routine care on patient-reported health outcomes was measured by the 36-item Short Form Health Survey (SF-36)[31] and the EuroQol Questionnaire—5-Dimension (EQ-5D).[32] The SF-36 was completed by the patient to measure how the patient perceives general health status. The EQ-5D was completed by the patient to measure how severe the patient perceived general health.

In the SF-36 and EQ-5D index, baseline refers to values collected at the end of the acute therapy phase, and the endpoint refers to values col-

lected at week 65 of treatment or at an early discontinuation visit between week 14 and week 65 of treatment.

Statistical analysis

All analyses were conducted on an intent-to-treat basis. Therapy effects were evaluated based on a two-sided significance level of 0.05, and interaction effects at 0.10. No adjustments for multiple comparisons were made. Application software (SAS, Version 8.0 SAS, Inc., Cary, NC) was used to perform all statistical analyses.

For categorical data, therapy group comparisons were made using Fisher's exact test. These include reasons for patient disposition, patient characteristics (e.g., gender, origin, types of diabetic mellitus), concomitant medication use, and safety endpoints (e.g., adverse events). For continuous data, therapy group comparisons were made using a type III sum-of-squares analysis of variance (ANOVA) model, with the terms of therapy and investigator. These include patient characteristics at baseline (e.g., age, height, and weight, duration of diabetes, duration of diabetic neuropathy, and Michigan Neuropathy Screening Score), duration of exposure, change from baseline for vital signs, ECG parameters, and ranked laboratory assessments.

Assessments of change from baseline for the MNSI, electrophysiology measures, and ranked microalbumin/creatinine ratio were made using a type II sum-of-squares ANOVA model with terms of investigator, acute therapy (duloxetine or placebo), extension therapy, and acute therapy by extension therapy. Testing the significance of the therapy factor in the extension phase was of primary interest. Ophthalmologic exams that summarized worsening in visual acuity and the types of procedures required during the study were analyzed using the Cochran-Mantel-Haenszel general association test, controlling for acute therapy.

For the EQ-5D index, and each of the SF-36 domains, including physical and mental component summaries, therapy-group differences in the mean change from baseline to endpoint were evaluated using a type III sum-of-squares analysis of covariance (ANCOVA) model with terms of baseline, investigator, and therapy in the model. In addition, investigator-by-therapy interaction was assessed by adding this term to the above model with a type II estimate approach.

RESULTS

Patient disposition, demographics, and disease characteristics

Two hundred thirty-seven patients who completed the acute therapy period were rerandomly assigned to therapy with either duloxetine 60 mg BID ($N = 161$) or routine care ($N = 76$). There were no statistically significant therapy-group differences observed in any of the patient demographics or disease characteristics (Table 1). The majority of the patients were male (61.2%) and Caucasian (78.5%). The mean patient age was 60 years and the mean MNSI score was 5.7. The mean duration of diabetes in all patients was 9.9 years with type 2 diabetes being the most prevalent (90%).

A total of 179 (75.5%) patients completed the extension phase of the study (116 [72%] duloxetine-treated and 63 [82.9%] routine care-treated group). The reasons for study discontinuation are summarized in Table 2. There were no statistically significant differences observed between routine care and duloxetine therapy for any of the reasons for discontinuation.

Concomitant medications

Table 3 summarizes concomitant medications used by at least 5% of patients. A statistically significant therapy-group difference was observed with regard to concomitant use of Neurontin (gabapentin), Lantus (insulin glargine injection), Amaryl (glimerpiride), and Lasix (furosemide). Neurontin (gabapentin) use was allowed only in the routine care-treated group. A significantly smaller percentage of duloxetine-treated patients reported taking these medications. The most frequently reported concomitant medications used by all patients were glucophage, aspirin, Avandia (rosiglitazone), Neurontin (gabapentin—for routine care-treated group only), Lipitor (atorvastatin), Tylenol (acetaminophen), and Actos (pioglitazone).

Table 4 presents medications used by patients in the routine care group for DPNP. The most commonly used pain medications for routine care-treated patients included Neurontin (gabapentin), Elavil (amitriptyline), Effexor-XR (venlafaxine extended release), and Tylenol (acetaminophen).

Table 1. Demographics and Baseline Assessments

Variable	*Duloxetine (N = 161)*	*Routine care (N = 76)*
Mean age, years, (SD)	59.7 (10.7)	60.6 (10.3)
Gender		
Female, *n* (%)	62 (38.5)	30 (39.5)
Male, *n* (%)	99 (61.5)	46 (60.5)
Race (origin)		
Caucasian, *n* (%)	128 (79.5)	58 (76.3)
Hispanic, *n* (%)	26 (16.1)	14 (18.4)
African, *n* (%)	4 (2.5)	2 (2.6)
Western Asian, *n* (%)	1 (0.6)	0 (0.0)
Other, *n* (%)	2 (1.2)	2 (2.6)
Mean weight, kg (SD)	101 (24)	105 (25)
Type of Diabetes Mellitus		
Type 1, *n* (%)	15 (9.3)	8 (10.5)
Type 2, *n* (%)	146 (90.7)	68 (89.5)
Mean duration of diabetes, years (SD)	10.3 (9.5)	9.3 (9.1)
Mean duration of diabetic neuropathy, years (SD)	3.9 (4.5)	3.1 (2.5)
Mean MNSI (SD)	5.6 (1.5)	5.8 (1.5)

MNSI, Michigan Neuropathy Screening Instrument; SD, standard deviation

Safety

Extent of exposure. The mean duration of exposure (days) was significantly longer ($p = 0.032$) for routine care-treated patients (mean days [standard deviation [SD]: 336.4 [70.8]) compared to duloxetine-treated patients (mean days [SD]: 304.2 [116.1]). The median duration was similar for both groups and was approximately 1 year. The total patient–years of exposure was 134.1 for the duloxetine-treated group and 70.0 for the routine care-treated group.

Deaths. During the study, 4 deaths (2 duloxetine-treated patients and 2 routine care-treated patients) occurred, which were considered by the investigators to be unrelated to the study drug or the protocol procedures. The cause of death in the 2 duloxetine-treated patients was myocardial infarction and acute myocardial infarction, and in the 2 routine care-treated patients was myocardial infarction and pulmonary embolism. The mortality rate per 100,000 patient–years was 1491.5 for the duloxetine-treated group, 2857.6 for the routine care-treated group, and 1960.0 for the combined population.

Serious adverse events. During the study, a significantly higher percentage of routine care-treated patients experienced 1 or more serious adverse events (SAE) (28.9% routine care-treated versus 16.8% duloxetine-treated; $p = 0.039$). A significant therapy group difference was also observed in congestive heart failure, with a higher

Table 2. Patient Disposition

	Duloxetine (N = 161) %	*Routine care (N = 76) %*
Completed 52-week study	72.0	82.9
Discontinued because of:		
Adverse event	9.3	2.6
Death	1.2	2.6
Unable to contact patient (lost to follow up)	3.7	3.9
Personal conflict or other patient decision	8.7	2.6
Physician decision	0.6	2.6
Protocol violation	1.2	0.0
Lack of efficacy	3.1	2.6

Table 3. Concomitant Medications Used by at Least Five Percent of Patients

Drug name	*Duloxetine (N = 161)* n %	*Routine care (N = 76)* n %
Glucophage	52 (32.3)	22 (28.9)
Aspirin	41 (25.5)	18 (23.7)
Avandia	29 (18.0)	17 (22.4)
Neurontin[a]	0 (0.0)	44 (57.9)
Lipitor	25 (15.5)	18 (23.7)
Tylenol	29 (18.0)	14 (18.4)
Actos	24 (14.9)	18 (23.7)
Lantus[b]	18 (11.2)	16 (21.1)
Amaryl[b]	17 (10.6)	16 (21.1)
Zocor	23 (14.3)	8 (10.5)
Glyburide	16 (9.9)	14 (18.4)
Calcium	19 (11.8)	8 (10.5)
Metformin	15 (9.3)	12 (15.8)
Multivitamin	17 (10.6)	10 (13.2)
Hydrochlorothiazide	17 (10.6)	9 (11.8)
Lasix[b]	12 (7.5)	14 (18.4)
Lisinopril	20 (12.4)	6 (7.9)
Atenolol	20 (12.4)	4 (5.3)
Vitamin E	14 (8.7)	10 (13.2)
Diovan	16 (9.9)	7 (9.2)
Glucovance	14 (8.7)	8 (10.5)
Humalog	12 (7.5)	7 (9.2)
Vitamin C	11 (6.8)	8 (10.5)
Altace	13 (8.1)	5 (6.6)
Glipizide	12 (7.5)	6 (7.9)
Plavix	12 (7.5)	5 (6.6)
Acetaminophen	13 (8.1)	3 (3.9)
Nexium	11 (6.8)	5 (6.6)
Glucotrol	11 (6.8)	4 (5.3)
Insulin	8 (5.0)	7 (9.2)
Toprol XL	11 (6.8)	4 (5.3)
Accupril	6 (3.7)	8 (10.5)
Furosemide	12 (7.5)	2 (2.6)
Synthroid	8 (5.0)	6 (7.9)
Amoxicillin	11 (6.8)	2 (2.6)
Prevacid	9 (5.6)	4 (5.3)
Coumadin	5 (3.1)	7 (9.2)
Flomax	10 (6.2)	2 (2.6)
Folic Acid	8 (5.0)	4 (5.3)
Norvasc	9 (5.6)	3 (3.9)
Pravachol	9 (5.6)	3 (3.9)
Protonix	7 (4.3)	5 (6.6)
Viagra	9 (5.6)	3 (3.9)
Zithromax	9 (5.6)	3 (3.9)

[a] $p < 0.001$.
[b] $p < 0.05$.

percentage of routine care-treated patients (5.3%) experiencing this event versus duloxetine-treated patients (0.6%).

Discontinuations because of adverse events. A total of 21 (8.9%) patients discontinued due to any adverse event (including death): 4 (5.3%) routine care-treated patients (1.3% occurrence of the following events: myocardial infarction, dementia, fall, pulmonary embolism), and 17 (10.6%) duloxetine-treated patients (0.6% occurrence of the following events: myocardial infarction, acute myocardial infarction, agitation, chest pain, coronary artery disease, diabetic ketoacidosis, dizziness, dyskinesia, frequent bowel movements, gamma-glutamyltransferase increased, hypercalcaemia, nausea, Parkinson's disease, pruritus, surgery, urinary retention, and vomiting).

Table 4. Summary of Medications Used by at Least Five Percent of Patients in the Routine-Care Group for Treatment of Diabetic Peripheral Neuropathic Pain

	Routine care (N = 76) n (%)
Neurontin	44 (57.9)
Elavil	11 (14.5)
Amitriptyline	6 (7.9)
Effexor-XR	9 (11.8)
Effexor	7 (9.2)
Tylenol	8 (10.5)
Carbamazepine	4 (5.3)

Treatment-emergent adverse events. Of the patients randomly assigned in the study, 221 (93.2%) patients reported at least 1 TEAE. There were no therapy-group differences in the overall incidence of TEAEs. The TEAEs that occurred with significant therapy-group differences included pain in extremity (15.8% versus 6.2%; $p = 0.029$), peripheral edema (15.8% versus 5.0%; $p = 0.010$), balance disorder (5.3% versus 0.6%; $p = 0.038$), erythema, feeling abnormal, and localized infections (3.9% versus 0%; $p = 0.032$). All of these TEAEs occurred at a higher rate in the routine care-treated group. No significant therapy-group differences in TEAEs occurred in which patients in the duloxetine-treated group experienced the highest percentage of events. In duloxetine-treated patients, the only TEAE reported by 10% or more of patients was nausea (10.6%). In routine care-treated patients, the TEAEs reported by 10% or more of patients were peripheral edema and pain in extremity (15.8%), somnolence (14.5%), and dizziness (13.2%). Most TEAEs were mild or moderate. There were no significant differences between therapy groups in the overall incidence of TEAEs that were classified as severe. A greater percentage of routine care-treated patients experienced pain in extremity, peripheral edema, and dyspnoea as severe and this difference was significant. There were no significant therapy-group differences observed in the treatment-emergent abnormal laboratory values at any time for blood chemistry and urinalysis.

Analysis of chemistry/urinalysis. Table 5 summarizes mean change in chemistry analytes and urinalysis from baseline to endpoint. There was a slight, but significant, therapy-group difference in mean change for aspartate transaminase, chlo-

Table 5. Mean (Standard Deviation) Change from Baseline to End Point in Laboratory Values

	N	*Duloxetine 60 mg BID*	N	*Routine care*
Alkaline phosphatase (U/L)	153	4.99 (22.24)	69	2.75 (14.39)
ALT/SGPT (U/L)	152	1.96 (12.40)	69	−1.48 (15.51)
AST/SGOT (U/L)[a]	150	1.96 (10.09)	69	−1.41 (12.72)
Bicarbonate, HCO_3 (mmol/L)	152	1.41 (3.00)	69	1.41 (2.82)
Total bilirubin (μmol/L)	152	−0.55 (3.08)	69	−1.07 (2.49)
Calcium (mmol/L)	153	−0.01 (0.12)	69	−0.02 (0.10)
Chloride (mmol/L)[a]	153	−3.14 (3.47)	69	−2.28 (3.30)
Cholesterol (mmol/L)	153	0.14 (1.10)	69	−0.11 (1.09)
Creatinine phosphokinase (U/L)	152	−6.93 (122.16)	69	−15.80 (127.23)
Creatinine (μmol/L)	153	−1.51 (16.04)	69	−1.28 (19.52)
GGT (U/L)	153	−0.10 (32.57)	69	−7.38 (37.85)
Glucose, fasting (mmol/L)[a]	152	0.30 (4.34)	69	−0.82 (4.45)
Inorganic phosphorus (mmol/L)	153	0.01 (0.19)	69	0.02 (0.18)
Potassium (mmol/L)	153	−0.02 (0.39)	69	−0.05 (0.41)
Sodium (mmol/L)	153	−1.16 (3.46)	69	−0.65 (2.68)
Total protein (g/L)	153	0.74 (3.52)	69	0.62 (4.13)
UA-PH (U)	134	−0.02 (0.79)	60	−0.13 (0.87)
UA-Specific gravity[a]	134	0.00 (0.01)	60	−0.00 (0.01)
Urea nitrogen (mmol/L)	153	0.19 (1.88)	69	0.32 (2.65)
Uric acid (μmol/L)[a]	153	−8.69 (61.82)	69	19.65 (77.16)
Urine albumin (mg/L)	118	18.55 (300.97)	56	11.64 (262.87)
Urine creatinine (mmol/L)	118	0.60 (6.27)	56	0.91 (7.34)

[a]Therapy-group difference $p < 0.05$.

BID, twice daily; QD, once daily; ALT/SGPT, alanine transaminase/serum glutamate pyruvate transaminase; AST/SGOT, aspartate transaminase/serum glutamic oxaloacetic transaminase; GGT, γ-glutamyl transferase.

ride, fasting glucose, urinalysis (UA) specific gravity and uric acid analytes. For aspartate transaminase, fasting glucose, and UA specific gravity, there was a mean increase in duloxetine-treated patients and a mean decrease for routine care-treated patients. For uric acid there was a mean decrease in duloxetine-treated patients and a mean increase in routine care-treated patients. For chloride, there was a mean decrease for both treatment groups and the mean decrease was greater for duloxetine-treated patients.

Analysis of HbA_{1c} and lipid profile. In the duloxetine therapy group, the only analyte with a slight but significant mean difference compared to routine care was mean high-density lipoprotein (HDL) cholesterol-dextran precip (HDL-DX) ($p < 0.001$). Both therapy groups experienced a decrease, with routine care patients experiencing a greater decrease (mean change [SD]: −0.13 [0.19]) versus duloxetine-treated patients (mean change [SD]: −0.02 [0.17]). No significant therapy-group differences were observed in HbA_{1c}, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Abnormal liver function tests. There were no patients who experienced treatment-emergent elevated bilirubin concomitant with treatment-emergent abnormal liver function tests. Three patients experienced an elevation in liver enzymes greater than 3 times the Covance upper limit of normal. Of these, two patients experienced an elevation in liver enzymes that were judged to be unrelated to the study drug. The third patient had elevated hepatic labs during the acute phase of the trial, which began to decline during the drug-tapering phase of the acute therapy period. When the patient entered the open-label extension phase and was rerandomized to routine care, the patient continued in the trial with no further elevations in hepatic analytes.

Diabetic complication assessments.

Neuropathy screening instrument: During the study, there were no significant therapy-group differences observed in the mean change in the MNSI score from baseline to endpoint.

Ophthalmologic examination: There were no significant therapy-group differences observed for any of the ophthalmologic examination measures. These measures included worsening of visual acuity (left or right), required procedures (macular laser surgery, panretinal photocoagulation, vitrectomy), reasons for photocoagulation (neurovascularization, vitreous hemorrhage, or other), and reasons for vitrectomy (vitreous hemorrhage, traction retinal detachment, or other).

Electrophysiology measure: There were no significant therapy-group differences observed for any of the electrophysiology measures for either subset of patients. These measures included ulnar F-wave, ulnar distal sensory latency, peroneal F-wave, peroneal CMAP from baseline to end point for a subset of randomly assigned patients with data from the same limbs and for all randomly assigned patients.

Microalbumin/creatinine ratio: There was a statistically significant therapy-group difference observed in the change in microalbumin/creatinine ratio from baseline to endpoint ($p = 0.027$). For the duloxetine therapy group, there was a mean increase in microalbumin/creatinine ratio (mean change [SD]: 0.05 [0.27]) that was not of a magnitude to be considered clinically relevant and patients continued to be well within normal limits at end point. Routine care-treated patients experienced a slight mean decrease (mean change [SD]: −0.01 [0.13]) from baseline to endpoint in this ratio.

Vital signs, physical findings, and other observations related to safety.

Sitting blood pressure: Duloxetine-treated patients experienced a statistically significant ($p = 0.049$) but slight mean increase in diastolic blood pressure (mean change [SD]: 1.39 [10.71]) compared to routine care-treated patients who experienced a slight mean decrease (mean change [SD]: −1.76 [11.74]). Duloxetine-treated patients also experienced a statistically significant ($p = 0.010$) but slight mean increase in pulse (mean change [SD]: 1.70 [11.82]) compared to routine care-treated patients who experienced a slight mean decrease (mean change [SD]: −2.30 [11.29]). These changes were not considered clinically relevant. There was no significant therapy-group difference observed in mean change of systolic blood pressure or weight.

Sustained elevation in blood pressure: One duloxetine-treated patient and no routine care-treated patients met the definition of sustained elevation in blood pressure and this difference was not statistically significant. The patient remained in the study.

Electrocardiograms: Routine care-treated patients experienced statistically significant mean

increases in QT interval (mean change [SD]: 5.08 [24.98]; $p = 0.05$), PR (mean change [SD]: 4.60 [17.62]; $p = 0.015$), and QRS (mean change [SD]: 3.82 [10.07]; $p = 0.026$) compared to duloxetine-treated patients. Duloxetine-treated patients experienced slight mean decreases in QT interval (mean change [SD]: −1.50 [25.26]) and PR (mean change [SD]: −0.81 [15.13]) and a slight mean increase in QRS (mean change [SD]: 0.97 [8.34]). These changes were not clinically significant, and there were no other ECG parameters that were significantly different between therapy groups. There were no significant therapy-group differences observed in potentially clinically significant Fridericia corrected QT (QTcF) intervals.

Health outcomes

Table 6 summarizes the analysis of mean change from baseline to endpoint on the SF-36 subscales and the EQ-5D. There were no statistically significant therapy-group differences observed in the SF-36 subscales or on the EQ-5D.

DISCUSSION

The effectiveness of duloxetine in the management of DPNP has been established in three 12-week (acute therapy phase) double-blinded clinical studies.[27–29] In these studies, duloxetine 60 mg QD and 60 mg BID demonstrated significant improvement compared to placebo on the 24-hour average pain severity score. In addition, patients who completed one of the 12-week acute therapy phase studies were rerandomized to duloxetine 60 mg BID or routine care for 52 weeks of open-label treatment in order to evaluate the safety of duloxetine over long-term administration.[33] A phase 3, long-term, open-label, parallel safety study of patients with DPNP was also performed, and the efficacy of duloxetine 60 mg BID and 120 mg QD was observed for up to 28 weeks in patients with DPNP via the Brief Pain Inventory (BPI) and the Clinical Global Impressions (CGI) of Severity scale and both doses of duloxetine reduced BPI and CGI-Severity scores.[34] All these studies have provided evidence that duloxetine is efficacious, safe, and tolerable in the management of DPNP.

In the study reported here, duloxetine was well tolerated and safely administered in patients with DPNP during the 52-week open-label extension therapy phase of this study. There were no significant therapy-group differences observed in any of the patient demographics or disease characteristics, indicating that the therapy groups were comparable. No significant therapy group differences were observed in the physical or mental component scores or in any of the SF-36 subscales or in the EQ-5D questionnaire. In a previous 52-week study of duloxetine in the management of DPNP,[33] duloxetine was significantly better on the bodily pain subscale

Table 6. Mean Change in Health Outcome Measures

	Duloxetine N = *149* *LS mean change (SE)*	*Routine care* N = *68* *LS mean change (SE)*	*Group difference in LS mean change from baseline*[a] *(95% CI)*
Short Form 36 Health Status Survey			
Mental Health	−4.18 (1.29)	0.03 (1.88)	−4.22 (−8.47, 0.04)
General Health Perceptions[b]	−3.58 (1.37)	−2.91 (2.00)	−0.66 (−5.2, 3.87)
Bodily Pain	−0.05 (1.78)	−3.88 (2.60)	3.83 (−2.07, 9.72)
Mental Component Summary	−3.26 (0.76)	−1.06 (1.11)	−2.21 (−4.71, 0.30)
Physical Component Summary	1.32 (0.73)	−0.56 (1.06)	1.87 (−0.53, 4.28)
Vitality	−2.54 (1.62)	−0.37 (2.37)	−2.17 (−7.54, 3.2)
Social Functions	−5.30 (1.81)	−4.29 (2.64)	−1.02 (−7, 4.97)
Physical Role Limit	1.65 (3.22)	0.12 (4.70)	1.53 (−9.14, 12.19)
Emotional Role Limit	−5.99 (3.20)	−5.12 (4.68)	−0.87 (−11.47, 9.72)
Physical Functioning	4.03 (1.90)	−0.08 (2.77)	4.11 (−2.17, 10.39)
Euro Quality of Life[c]	−0.02 (0.02)	−0.05 (0.03)	0.02 (−0.04, 0.09)

[a]Differences in least square (LS) means = Duloxetine LS Mean − Routine Care LS Mean.
[b]Therapy-by-investigator interaction: $p = 0.094$.
[c]Therapy-by-investigator interaction: $p = 0.010$. Both interactions were attributed to outlying data for 3 patients from a single site. Qualitative inferences were similar when this site was excluded from the analysis.

of the SF-36 Health Status Survey, and duloxetine-treated patients perceived their general health to be better than routine care-treated patients as measured by the EQ-5D version of the Euro Quality of Life instrument.

Routine care-treated patients had a longer mean duration of exposure compared to duloxetine-treated patients. This may have been because routine care-treated patients were allowed to switch therapies without discontinuing from the study, whereas patients in the duloxetine therapy group could not be prescribed certain other treatments. There were no significant therapy-group differences observed in the overall incidence of TEAEs. Most TEAEs were mild or moderate in severity, and the TEAE reported by 10% or more of duloxetine-treated patients was nausea whereas in routine care-treated patients was peripheral edema, pain in extremity, somnolence, and dizziness. These findings are consistent with the known side effect profiles of duloxetine and gabapentin, the most commonly used drug in the routine care-treated group. Nausea was also the most frequently reported TEAE in the acute therapy phase studies, although nausea tended to appear early in treatment and subside quickly. Hypertension was reported as a TEAE in 3.1% duloxetine- and 2.6% routine care-treated patients. A significantly higher percentage of routine care-treated patients experienced 1 or more SAE with the single event congestive heart failure. Two routine care-treated patients reported hypertension as a SAE. There were no significant therapy-group differences observed in the overall incidence of discontinuation due to adverse events or for any single event.

The reported death rate of 1960.0 (per 100,000 patient–years) is about twice as high as the age adjusted death rate of 853.3 for all causes between 2000 and 2002.[35] The risk for death among people with diabetes is about two times that of people without diabetes.[36] Thus, the observed death rate in this study is what would be expected of a population of patients with diabetes, and may actually be lower than expected if one considers that disease in these patients is more likely to be more advanced than in the overall diabetic population. The observation that the death rate in the routine care-treated group was about twice as high as in the duloxetine-treated group is probably an artifact related to the low number of events.

Although duloxetine-treated patients experienced significant mean changes in a few chemistry analytes, these were not associated with clinical findings and these changes were of insufficient magnitude to have clinical relevance or represent systemic drug toxicity. Transaminase increases were not associated with increases in bilirubin. Duloxetine did not appear to adversely affect glycemic control or lipid profiles. The use of duloxetine appears to be associated with a small increase in fasting glucose in this study, similar to that seen in an earlier study.[34] None of these changes in analyte concentrations were of sufficient magnitude to have clinical relevance. Overall diabetes control does not appear to be affected, as evidenced by the lack of any meaningful changes in HbA_{1c}.

Duloxetine-treated patients experienced a slight, but significant mean increase in diastolic blood pressure and pulse compared with routine care-treated patients. Neither of these effects was considered clinically relevant. No significant therapy-group differences were observed in sustained elevation in blood pressure. The observed increase in pulse rate for the duloxetine-treated patients could be expected due to elevations in NE tone.[37] These results are supportive of earlier clinical trials with duloxetine[22–25,27–29] and suggest that duloxetine has a safe cardiovascular profile. Routine care-treated patients experienced significantly higher mean changes in QT, PR, and QRS intervals compared with duloxetine-treated patients. No other ECG parameters were significantly different between therapy groups, and no significant therapy-group differences were observed in potentially clinically significant QTcF intervals. The lack of significant cardiovascular changes due to duloxetine therapy in these patients suggests that patients with diabetes mellitus do not require more intensive assessment of their cardiovascular status when treated with duloxetine, than they require for their underlying diabetes. There were no significant therapy-group differences observed in the MNSI, ophthalmologic, and electrophysiologic measures. The diabetic complications assessments demonstrated that duloxetine does not appear to adversely affect nerve function or the course of DPNP, nor does it change the progression of retinopathy.

Although caution must be used when interpreting results in an open-label study, the results of this trial corroborate previous studies that duloxetine is safe and well tolerated in the management of patients with DPNP. In the previously

reported 52-week study comparing duloxetine 60 mg BID to routine care in the management of DPNP, duloxetine performed as well as routine care on most measures of safety, and the duloxetine-treated group had significantly higher scores on the SF-36 bodily pain subscale and on the EQ-5D.[33] In the earlier study, there were no adverse events that were reported significantly more frequently in duloxetine-treated patients compared with routine care-treated patients. The study reported here provides additional evidence that duloxetine is safe for long-term therapy of patients at least 18 years old diagnosed with DPNP, and the overall safety profile reported here appears to be similar to that observed in major depressive disorder patients[22–25,38] as well as in that observed in other double-blind placebo-controlled studies of duloxetine in patients with DPNP.[27,28]

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